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# PUBLIC HEALTH REPORTS.

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[Reports to the Surgeon-General Public Health and Marine-Hospital Service.]

## *Professor Kolle's researches on plague.*

[By W. HAVELBUG, M. D., late sanitary inspector, U. S. Marine-Hospital Service, at Rio de Janeiro.]

BERLIN, GERMANY, *July 20, 1902.*

The learned investigator, Professor Kolle, who has done so much in regard to plague, has published in various scientific journals and societies' transactions his results regarding the plague bacillus, and plague serum, and as these communications have not only high scientific value, but also a highly practical equivalent, one may be excused for giving an abstract of the same in these reports.

### I.—*Virulence of plague cultures and criteria for their recognition.*

One of the most important advances in the diagnostic use of animal experimentation should be considered the method of cutaneous infection of guinea pigs. This method has not only a theoretical and diagnostic value, but has at the same time proved an excellent means for the general estimation of virulence in general, and of low virulence in particular.

The method is the following: The skin over a portion of the abdominal wall of the guinea pig is shaved, care being taken to avoid the slightest injury to the skin. The infective material is carefully rubbed into the shaved skin. Important, in order to rightly understand the occurrence of plague infection, is the fact disclosed here in the case of guinea pigs, that by this method of inoculation the animals present the picture of true bubonic plague—that is to say, the production of nodules in the various organs, principally in the spleen. In this manner guinea pigs, which would not be affected by large subcutaneous injections, even amounting to 2 mg. of agar culture (equal to a loop) of low virulence plague bacillus, may be infected and eventually succumb.

It has been found by repeated experiments that certain modifications of virulence which are unrecognizable in any other animal can be definitely appreciated in guinea pigs in which a certain area of the abdominal wall has been shaved and into which has been rubbed a definite quantity of a culture, viz, of a one-fifth loop, mixed with .2 c. c. bouillon.

That cultures should be maintained at the highest virulence is not only important for the production of vaccines for the purpose of prophylactic vaccinations, but also for the preparation and calibration of plague serum. Bacilli isolated from plague-infected men soon lose their virulence unless they are passed through animals. The most suitable are rats. In fact, without passage through rats it is impossible to maintain a culture at high virulence.

Batzaroff found that the most virulent plague germs were to be obtained from the pneumonic lungs of rats which have been infected through the nasal aperature by infected cotton wool. Kolle and his colleague, Martini, have verified this statement. They found, however, that this method of infection is not a constant one. Martini has therefore constructed an inhalation apparatus by which he succeeded without fail in producing pneumonia. Twenty animals can at one time be dealt with under the fittingly closed bell glass of the apparatus, into which fluid containing plague culture is spread. The manipulation of the apparatus is entirely without danger to the operators. The most virulent cultures obtainable are those derived by the passage of bacilli through a series of rats so treated. Such cultures so obtained are not second to those from fresh human plague.

### II.—*Chronic form of plague in rats.*

It is not sufficiently recognized in laboratory experiments that a chronic form of plague exists in rats. From an epidemiological point of view it is of great importance to observe that such chronic infection often occurs. Careful post-mortem examinations on rats, months before inoculated, no matter how, show chronic pathological changes, such as incapsuled caseous nodules in the submaxillar glands, caseous bronchial glands, and fibroid induration of the lungs. In all such cases can virulent plague bacilli be demonstrated, either by culture method or in animal inoculation. Such observations are of the utmost importance for the epidemiologist.

### III.—*On the diagnosis of plague.*

The diagnostic value of cutaneous infection of guinea pigs is especially seen in cases where the plague bacilli are to be demonstrated from the corpses or decomposing fluids or suspected material, in which but a few germs are present, such as the blood in chronic cases, in all of which the virulence might be too low to infect rats. This method of cutaneous infection of guinea pigs has further the advantage over regular infection experiments on rats in as much as it not only allows the recognition of an extremely small number of germs, but also to a certain extent excludes the accompanying germs of decomposition. The shaved skin acts just like an agar plate, not only multiplying the germ in the body of the guinea pig, but what is more important, produces a pure culture of the same.

The great responsibility, which falls on the authorities, in arriving at a correct diagnosis of plague, especially in the first outbreak, necessitates a thorough preparation of the material and a completeness of technic, which is sketched out in the following :

A. Plague with buboes. With fluid, obtained either by means of syringe or through the opening of an abscess, are prepared : 1. Cover-glass preparations. 2. Cultures on agar plates and agar tubes. 3. Cultures in bouillon tubes, to be used later for inoculation of guinea pigs and rats. 4. Allow a few drops of the fluid to fall on the conjunctiva of 4 to 6 rats. 5. Subcutaneous inoculation of 4 to 6 rats with 1 drop of the fluid, if necessary, diluted with bouillon. 6. Apply the fluid to the shaved abdominal skin of 4 to 6 guinea pigs.

B. Plague without manifest buboes. The bacilli are in such cases generally difficult to demonstrate. 1. Pneumonia-plague. Treat the sputum according to A 1 to 6. 2. Should the suspicion exist of pneumonia plague, in which no sputum is obtainable, then should the blood be at once carefully examined. This is done by extracting a drop of blood from the finger every second hour and inoculating agar tubes with the same. Further, should larger quantities (30 to 40 c. c.) be extracted by means of vivisection and collected in a sterile vessel and defibrinated; with the fluid thus obtained are inoculated (*a*) rats in the conjunctiva, into the peritoneum and subcutaneously inoculated (1 to 2 c. c.). (*b*) Guinea pigs on the shaved abdominal skin; (*c*) 10 to 20 agar plates smeared with 0.5 to 1 c. c. (*d*) Three flasks, containing 50 c. c.; bouillon each, inoculated with 1 to 2 c. c. of the fluid. 3. Tonsillar plague. Preparations from the tonsils should be made according to A 1 to 6.

C. By convalescents from plague (without local symptoms); 1. Extraction of blood by means of cupping instruments, for the purpose of determining the serum reaction. 2. Examination of the sputum and pharyngeal phlegm by means of cultures and inoculation of guinea pigs and rats.

D. Examination of the bodies of suspected rats.

1. In fresh, not decomposed bodies, careful necropsy should be made and preparation of the lymph glands, especially of the submaxillar and auricular glands. (*a*) Microscopical examination from the spleen, blood, and enlarged glands. (*b*) Inoculation of agar plates. (*c*) Inoculation of rats and guinea pigs, B 2 as above. (*d*) Feed rats on the cadaver.

2. By decomposed bodies of rats, fæces, etc., make a necroscopic microscopical preparation from any hemorrhagic glands that may exist; application from as much liquid of the glands as possible, from spleen emulsion or fæces on the shaved abdominal skin of guinea pigs.

E. Human plague bodies. (*a*) Fresh necroscopic preparation of material according to A 1 to 6. (*b*) Decomposed bodies. Treat according to D 2.

F. Suspected foul debris may be moistened with water and applied to the shaved skin of guinea pigs.

### IV.—*Experiments with plague serum.*

It is well known that the great expectations hoped for from Yersin's serum have not been realized. The slight curative effect of this serum has been acknowledged also by French authors, and it has been recommended that the serum no longer be subcutaneously but intravenously employed. Lately, however, a more potent serum has been prepared in the Pasteur Institute, which has been used in treating plague patients in South America, Oporto, Alexandria, and Cape Town, without, however, any marked results. In India, since the failure of the first and second French serum, prepared in Pasteur's Institute, that of Lustig has been used. Reports from the medical authorities at Bombay showed that the serum possesses a marked curative action in the lighter cases of plague. In severe cases no serum as yet has succeeded. Indeed, injections of as much as 3 liters of serum have failed to save the patients.

Under these circumstances the efficacy of plague serum must, in the main, be proved by researches in animals. The value of the plague serum, produced as it is in great quantities by the Pasteur Institute in Paris from about 40 immunized horses, and from thence distributed over the whole world, may be more readily investigated, as in the case of plague. Not only men, but rats, mice, monkeys, guinea pigs, suffer either spontaneously or epidemically from this disease.

From this standpoint Professor Kolle has investigated the antipest serum of the Pasteur Institute with over 500 animals, with numerous collateral controls with normal serum. The animals employed were rats, guinea pigs, and mice. The observations were mainly made on mice, because in Pasteur's Institute it was on these animals that the efficacy of the plague serum is tested in the following manner: A fine syringe needle, dipped into a diluted emulsion of bacilli, is plunged into the roots of the tail. The serum is injected either subcutaneously or intraperitoneally twenty-four hours before the infection is made. In this case, therefore, we are dealing with the examination of the serum only with regard to the protective bodies contained in it.

Kolle's experiments varied to the utmost possible extent. Cultures of the highest, as well as those of lesser virulence, were employed. Subcutaneous injections, injections into skin folds, and simple punctures, intraperitoneal injections, subconjunctival inoculations, and inoculations on the shaved abdominal wall, were carried out. The serum was sometimes subcutaneously, at others intraperitoneally, injected in doses of 0.4, 4 c. c. for rats; 0.5, 6 c. c. for guinea pigs; 0.05, 1 c. c. for mice. Some of these injections were made before the infection in order to observe the protective influence of the serum, others contemporaneously and at varying periods after the infection.

The curative effects of plague serum on animals infected with highly virulent cultures, no matter how the infection may be made, is by all three types of animals examined extremely slight, anyhow in as much as the life of the animals is concerned. All three animal types succumb to cultures of lesser and low virulence when the serum was given later than twenty-four hours after the infection, or when the animals showed signs of ailing before the serum injection was made. In almost all cases, however, the serum prolongs life somewhat.

The curative effects on mice can not be however denied when cultures of low virulence are employed; with these animals, it must be stated, that the results are rarely constant, which must be attributed to variable individual susceptibility.

One can not be too careful in avoiding the drawing of far-reaching conclusions as regards men from these animal experiments with cultures of low virulence, for in the case of plague-infected men it is not with a low but with extremely high virulent bacteria that they are infected. It is obvious from the grave clinical course of the disease so ending, as it does, in death, further from the fact that the majority of the bacilli isolated from plague deceased are of such virulence as to immediately kill the animals infected with them.

### *V.—Specific bactericidal substances in the plague serum.*

The effective power of the serum must to a great extent be ascribed to specific bacteriolytic bodies present in it. If subcutaneous injections are made on guinea pigs or rats with 1 to 2 c. c. plague serum and if after about twenty-four hours 2 to 3 loops of low virulent bacilli mixed with physiological salt solution is injected in the peritoneal cavity, then one can observe in hanging drop preparations of fluid withdrawn from the peritoneum by means of capillary tube three to four hours later, a complete dissolution of the bacteria. We have therefore to do in plague serum with one of those substances, first accurately described by R. Pfeiffer and which we call bactericidal or antiinfectious. Such a body is analogous to those which have already been described in typhoid, cholera, and pyocyaneus sera. There is much ground for believing that with the exception of the bactericidal power in the serum, no other, such as antitoxic, exists in it. A most important fact, however, is that both in men and animals when symptoms typical of poisoning, such as collapse, etc., occur the serum is powerless to combat these symptoms, and if it has any effect whatever it is rather in destroying those bacteria existing in the circulation and tissues, and in so doing liberating the poison contained in them, and thus possibly doing more harm than good.

### VI.—*Agglutination experiments.*

The serum is supplied by the Pasteur Institute both in dry and in fluid condition. If dried, it is mixed with 10 times its volume of sterile water in order to dissolve it, which takes three to four hours. Such dried serum forms an excellent means of carrying out observations on agglutination.

In spite of the powerfully agglutinizing properties of the dried, as compared with the fluid serum, it has no stronger healing effect, as over 60 experiments on varied types of animals have proved. The agglutination property of the serum is absolutely specific. Experiments with the bacilli typhonurium, fowl cholera, hog cholera, hog plague, pseudotuberculosis, bacillus Danysz, all bacilli which not only are similar, inasmuch as they produce hemorrhagic septicæmias, but are also morphologically akin, prove that the plague serum agglutinizes none of these. Only plague bacilli are affected, and these even in a dilution, greatest 1 to 6000, no matter how or where the bacilli are obtained.

To demonstrate agglutination quantitatively, one must take certain precautions. The best procedure is the following: Dilutions are made with 0.8 per cent salt solution of 1 to 10, 1 to 50, 1 to 100, 1 to 200, 1 to 300, 1 to 400, 1 to 500. 1 to 1,000. One cubic centimeter from each is put into a sterile tube. Series of tubes have thus been prepared, each containing 1 c. c. of fluid, in which 0.1, 0.05, 0.01, 0.005, 0.001 of serum is dissolved. Into each of these tubes is placed a loop full of bacilli, obtained from agar culture, and in which all lumps have been reduced to powder by rubbing the contents of the loops against the side of the glass. The phenomenon is best observed either by looking from above downward on a black ground, or upward in reflected daylight. In this manner it is easy to see the formation of clumps. The above method has advantages over the microscopical, because, in the latter scattered groups of bacteria, lying in merely biological relationship, as zooglœaform, and not separated by the manipulation, may be mistaken for the phenomenon of agglutination.

The reaction of agglutination should be easily recognizable with the naked eye in less than five minutes. The reaction is hastened by temperature of 35°. By the specific reaction the clump formation should be an ever increasing one.

Seeing that the reaction is so absolutely specific, the dried serum of the Pasteur Institute becomes a most valuable means for distinguishing the plague bacillus from its allies. Especially is it valuable in those cases, when the plague bacilli, having lost their virulence, are no longer capable of affecting the animals inoculated. Plague serum, through this property, has greater advantages in recognizing the bacillus than other characteristic culture appearances as the existence of branching, the involution forms on salt agar, the border formation of the colonies on agar culture and the growth at low temperature (0.5° C). A single successful agglutination experiment with a control allows one to arrive at once at an opinion. (In the same manner it can be assumed that when the serum of either men or animals exhibits the agglutination phenomenon, at some time they must have been infected with plague bacilli.) This agrees with the observations of the German commission in India, who stated that when the serum in dilution of 1 to 3 or 1 to 5 produces agglutination, the person is either suffering or recovering from plague.

It must be added, however, that only a small number of plague patients and convalescents exhibit this reaction of agglutination.

W. HAVELBURG, M. D.

### *The so-called "spotted fever" of the Rocky Mountains—A new disease in Bitter Root Valley, Mont.*

Surg. J. O. Cobb, of the U. S. Public Health and Marine-Hospital Service, was directed by Bureau telegram on June 23 to proceed to Missoula, Mont., in order to investigate an outbreak of the so-called "spotted fever" prevailing in that district. These orders were given as a result of information which was received from various sources that a new and strange disease prevailed in the Bitter Root Valley of Montana. The disease was said to be highly communicable, and, therefore, a matter of importance to the public health of the country.

Dr. Cobb's interesting report which follows has purposely been made brief and many interesting facts omitted because he found Dr. Louis B. Wilson and Dr. Wm. M. Chownning, representing the Montana State board of health, already on the field. These two scientists had, prior to Dr. Cobb's arrival, worked out many of the details concerning the cause of the disease and its method of transmission, which have since been published in The Journal of the American Medical Association (vol. 39, No. 3, p. 131). The report of Surgeon Cobb follows:

PORTLAND, OREG., *July 1, 1902.*

SIR: Complying with Bureau telegram of June 23, I proceeded to Missoula, Mont., to investigate an outbreak of so-called "spotted fever."

For a definite number of years (17) the disease has been known among the local practitioners of the Bitter Root Valley, and tradition reports from year to year back to the earliest settlements among the whites. So far as I could learn there have never been cases or fatalities from the disease among the Indians.

The disease has always been limited to the spring months, no case being reported later than July 20, and none earlier than 1 case on uncertain date in January. There is some doubt attached to the January case, which is supposed to have occurred several years ago. Usually the first cases appear in March, shortly after the first warm days. Every one with whom I talked is unanimous in the positive statement that the disease only occurs in the spring months, including, of course, the few warm days in March. In a few instances the disease has appeared in February, but in every case the month was very mild, having a number of warm days.

All clinical experience goes to show that the disease is not contagious or infectious. It is, therefore, without doubt, an inoculable disease, as an intra-corpscular parasite has been found constantly present in the blood of each examined case this year. The organism resembles very closely Theobald Smith's Texas cattle fever organism, and it is certainly reasonable to believe, from the knowledge at hand, that this disease is introduced in man in the same way and in like manner as in the Texas cattle fever organism, viz, by the tick.